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# Granisetron, an antiemetic drug, and its cobalt complex

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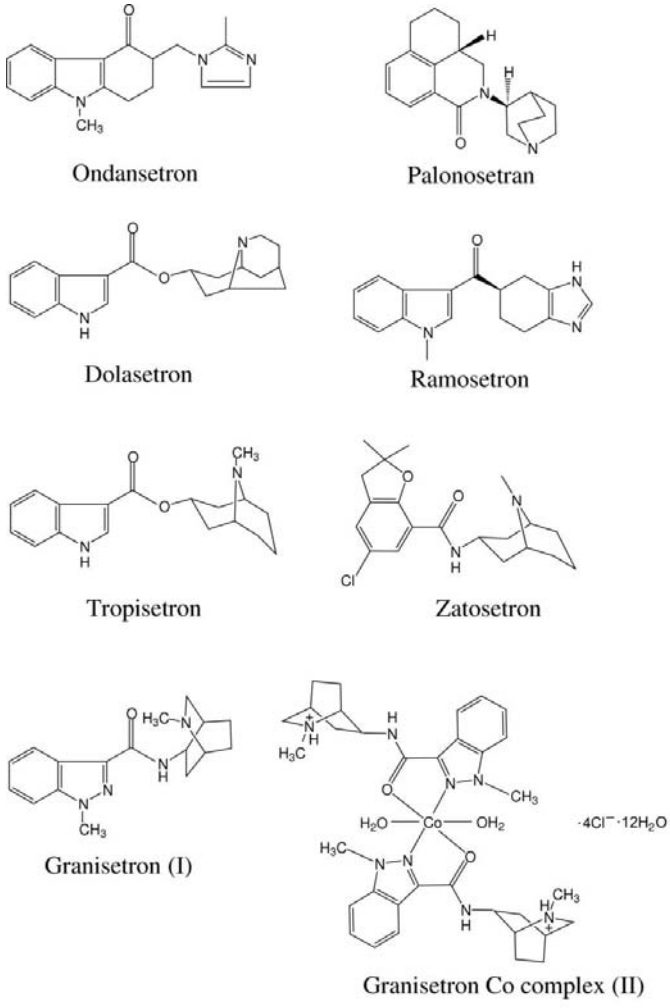
The crystal structures of granisetron [systematic name: 1-methyl-*N*-(9-methyl-9-azabicyclo[3.3.1]nonan-7-yl)indazole-3-carboxamide], $C_{18}H_{24}N_4O$, (I), an antinauseant and antiemetic agent, and its $Co^{II}$ complex, diaqua[1-methyl-*N*-(9-methyl-9-azoniabicyclo[3.3.1]nonan-7-yl)indazole-3-carboxamide]cobalt(II) tetrachloride dodecahydrate, $[Co(C_{18}H_{25}N_4O)_2(H_2O)_2]Cl_4\cdot 12H_2O$, (II), have been determined by X-ray diffraction. The granisetron molecule is in an extended conformation in both structures. Twisting of the central carboxamide group facilitates the $Co^{II}$ coordination in (II). The $Co^{II}$ atom is located on an inversion centre. The azabicyclononane ring adopts a chair–boat conformation in both structures. The molecules in (I) are linked into centrosymmetric dimers and form tetracyclic rings through C—H···O hydrogen-bonding interactions. The simultaneous presence of free chloride ions in conjunction with a number of hydration water molecules in (II) provides interesting hydrogen-bond patterns. This study can aid in the investigation of the properties of metal complexes with active pharmaceuticals in which the drug molecules play the role of a ligand.

## Comment

As their name implies, 5-$HT_3$ antagonists prevent serotonin from binding to 5-$HT_3$ receptors. Such receptors are present mostly on the ends of afferent branches of the vagus nerve, which sends signals directly to the brain's vomiting centre in the medulla oblongata, and in the chemoreceptor trigger zone of the brain, which receives input from nausea-inducing agents in the bloodstream and communicates with the vomiting centre. By preventing activation of these receptors, 5-$HT_3$ antagonists interrupt one of the pathways that lead to nausea and/or vomiting. All 5-$HT_3$ antagonists are identified by the setron, according to WHO's Anatomical Therapeutic Chemical Classification System, and are classified among antiemetic agents. Although these agents share a common mechanism of action in preventing chemotherapy-induced nausea and vomiting (CINV), there are differences in their pharmacological profiles. The major differences are found in their chemical structure, 5-$HT_3$ receptor affinity, dose–response curve and pharmacokinetic profile (Gan, 2005).




Granisetron, BRL 43694, is an indazole derivative developed by the British drug company Beecham (Sanger & Nelson, 1989; Plosker & Goa, 1991). It is unique among the 5-$HT_3$ receptor antagonists because it is not metabolized *via* the cytochrome P450 (CYP) 2D6 pathway (Tan, 2003). Granisetron is well tolerated with adverse events of mild severity including headache, asthenia and constipation. Overall, data demonstrate that granisetron is an efficacious, safe and cost-effective member of the 5-$HT_3$ receptor antagonist class for the prevention of CINV. Granisetron is usually administered as a hydrochloride salt and is produced by Hoffmann–La Roche under the trade name Kytril. It was approved in the UK in 1991 and in the US in 1994 by the Food and Drug Administration.

Several drugs have chelating properties. When co-administered with nutritional supplements, *viz* vitamins and minerals, chelating drugs can combine with metal ions in the gastrointestinal tract to form complexes that are poorly absorbed. Hence, attempts have been made to form metal-coordinated complexes with biologically active molecules, to

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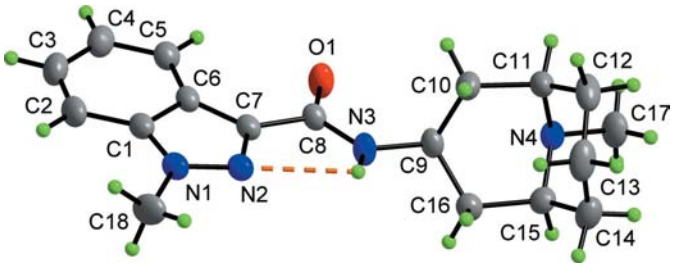



**Figure 1**
A view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. The intramolecular hydrogen bond is drawn as a dashed line.

try to improve their properties in terms of potency, stability, reduced side effects, or targeted delivery.

As part of our structural studies on pharmaceutical compounds (Ravikumar & Sridhar, 2006*a*,*b*, 2007*a*,*b*; Ravikumar *et al.*, 2008; Sridhar & Ravikumar, 2009) and stimulated by the studies on drug–metal interactions, the crystal structures of granisetron, (I), and its cobalt complex, (II), were determined.

The molecular structures of (I) and (II) are shown in Figs. 1 and 2, respectively, while selected geometric parameters are presented in Tables 1 and 3. The overall structure of the granisetron molecule in (I) and (II) may be described as a planar indazole ring linked by the coplanar carboxamide group to the flexible azabicyclononane ring system. In both (I) and (II), the two stereogenic centres, *viz*. C11 and C15, have the same relative configuration, corresponding to the *RS*/*SR* diastereoisomer. The granisetron moiety in each structure is in an extended conformation [C7—C8—N3—C9 = −179.65 (13)° in (I) and 177.58 (18)° in (II)]. A striking difference between the two structures is the orientation of the central carboxamide group. In chelating granisetron, (II), the carboxamide group is in a *cis* orientation, while in the free form, (I), it is *trans*. The metal coordination in (II) leads to a significant change in the bond angles around atoms C7 and C8. Also, the intramolecular N3—H···N1 hydrogen bond seen in (I) is not observed in (II). The $Co^{II}$ coordination polyhedron is a slightly distorted centrosymmetric octahedron, with the $Co^{II}$ ion at the centre of inversion. The distortion arises from the O1*W*—Co—O1*W*$^{i}$ axis which is not perpendicular to the coordination plane [O1/N2/O1$^{i}$/N2$^{i}$/Co; symmetry code: (i) −*x*, −*y* + 1, −*z* + 1]. The two bidentate ligands lie *trans* to one another and are coordinated to the $Co^{II}$ ion through the indazole N2 atoms and the carboxamide O1 atoms, forming a five-membered ring in the equatorial plane. Two O1*W* water atoms complete the octahedron at the axial positions. An overlay of the granisetron molecules of (I) and (II) with an analogous structure, (III) (the azabicyclo[3.3.1]nonane ring is replaced by an azabicyclo[3.2.1]octane ring at N3; Fludzinski *et al.*, 1987), superimposing the planar indazole systems, reveals the conformational flexibility (Fig. 3).

The conformation of the azabicyclononane ring system expressed by the torsion angles C—C—N4—C and N4—C—C—C in (I) and (II) is chair–boat. The protonation at N4 of

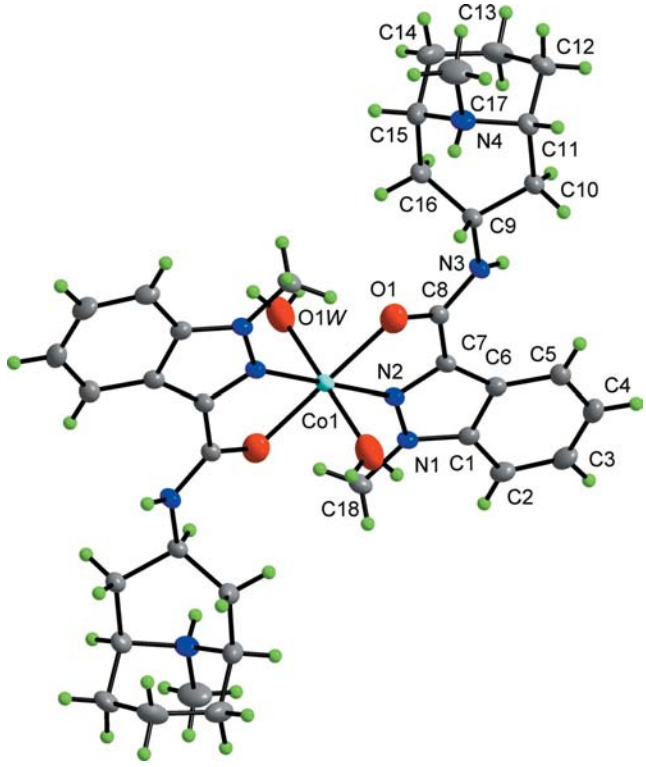



**Figure 2**
A view of the cobalt complex, (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. Unlabelled atoms are related to labelled atoms by an inversion centre at (−*x*, −*y* + 1, −*z* + 1). Noncoordinating water molecules (O2*W*, O3*W*, O4*W*, O5*W*, O6*W* and O7*W*) and chloride ions (Cl1 and Cl2) have been omitted for clarity.

the azabicyclononane ring (quinuclidinium) in (II) does not additionally influence its conformation.

The crystal packing in (I) is influenced by the centrosymmetric C—H···O dimerization between carboxamide atom O1 and atom C5 of the indazole ring (Table 2). The dimers are further linked by a C—H···O hydrogen bond formed by atom C18 of the azabicyclononane ring with carboxamide atom O1, resulting in a cyclic centrosymmetric tetramer resembling a square-grid mesh (Fig. 4). The presence of water molecules

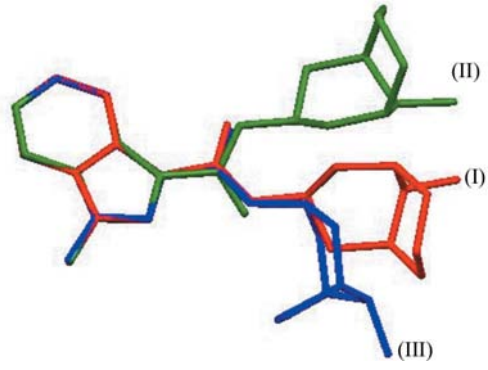



**Figure 3**
A superposition of the molecular conformation of the granisetron molecules of (I), (II) and an analogous compound, (III) (Fludzinski *et al.*, 1987). The overlay was made by making a least-squares fit through the indazole ring system of (I). R.m.s. deviations (Å) are as follows: (II), 0.062; (III), 0.016. H atoms have been omitted for clarity.

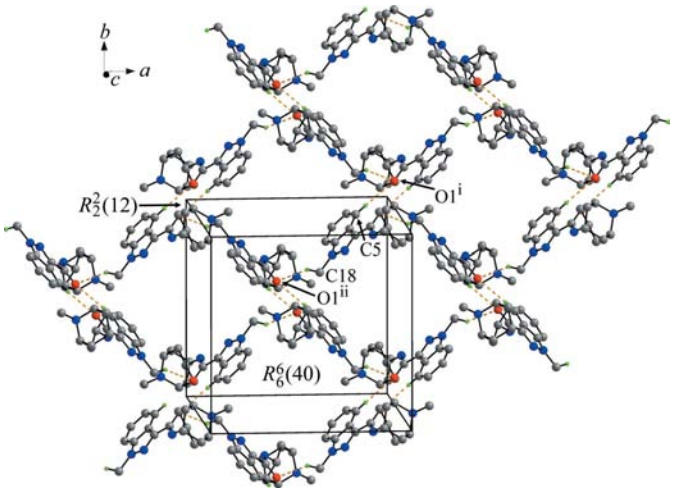



**Figure 4**
Part of the crystal packing of (I), showing the formation of the centrosymmetric tetramolecular $R_6^6(40)$ and dimeric $R_2^2(12)$ ring motifs (Etter, 1990; Etter *et al.*, 1990; Bernstein *et al.*, 1995) through C—H···O hydrogen bonds, resembling a square-grid mesh. Hydrogen bonds are shown as dashed lines and H atoms not involved in hydrogen bonding have been omitted for clarity. Selected atoms are labelled, primarily to provide a key for coding of the atoms. [Symmetry codes: (i) $2-x, 2-y, -z$; (ii) $-\frac{1}{2}+x, \frac{3}{2}-y, -z$.]

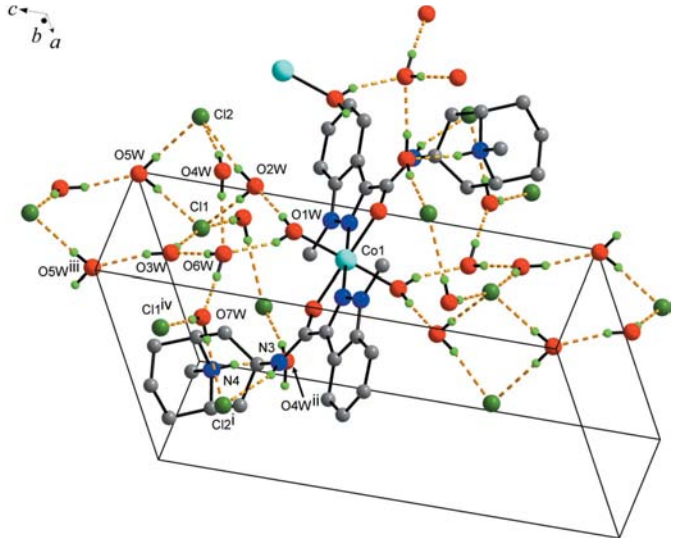



**Figure 5**
Part of the crystal packing of (II), showing the framework architecture formed by the combination of $Co^{II}$ coordination and hydrogen-bonded assemblies of chloride ions and water molecules. Hydrogen bonds are shown as dashed lines and H atoms not involved in hydrogen bonding have been omitted for clarity. Selected atoms are labelled, primarily to provide a key for coding of the atoms. [Symmetry codes: (i) $x+1, y+1, z$; (ii) $x+1, y, z$; (iii) $-x, -y+1, -z+2$; (iv) $x, y+1, z$.]

and chloride ions in (II) provides a unique medium for hydrogen bonding (Table 4). All water molecules act as both donors and acceptors and, along with chloride ions, form different O*W*···Cl ring clusters (Fig. 5). These pseudo-ring patterns are fused and form a continuous hydrogen-bonding network. The granisetron ligands connect the above-mentioned ring patterns through the amide (N3—H···Cl2$^{i}$) and protonated atom N4 of the azabicyclononane ring (N4—H···O4*W*$^{ii}$) (symmetry codes as in Table 4). The crystal packing of (II) thus exhibits a framework architecture formed by the combination of coordination and hydrogen-bonded assemblies of chloride ions and water molecules. Weak C—H···O and C—H···Cl interactions are also observed.

A number of pharmacophore models and alignments of antagonists binding to the 5-$HT_3$ receptors have been proposed (Hibert *et al.*, 1990; Lopez-Rodriguez *et al.*, 1997). It appears that 5-$HT_3$ receptor antagonists can share a pharmacophore, made up of the structural features of an aromatic moiety, a coplanar carbonyl function (with the O atom situated at an approximate distance of 3–4 Å from the centroid of the aromatic ring) and a basic N atom (situated at an average distance of 5.5 Å from the O atom of the carbonyl group and 7–8 Å from the centroid of the aromatic ring) which is almost aligned in the same plane as the aromatic ring. Comparing the present structures of (I) and (II) with those of other setrons (Chandra Mohan & Ravikumar, 1995; Ravikumar & Sridhar, 2007*b*) in the light of the above pharmacophore model, the geometric parameters deduced are listed in Table 5. Significant similarities in these derived structural parameters can be seen. However, it is difficult from this limited set of data to suggest which structural parameters contribute to the observed pharmacological differences. Considering the diversity seen in the chemical structure of the setrons, the structural features observed may still be useful for the further development of 5-$HT_3$ receptor antagonists.

In conclusion, the crystal structures of free granisetron, (I), and its cobalt complex, (II), reveal the rotational flexibility of the carboxamide group. An interplay of hydrogen-bonding interactions between the water molecules of hydration and chloride ions in (II) may mimic those found in solution for the salt or solvated molecule of (I).

## Experimental

Crystals of granisetron, (I) (Pharmacology Department, IICT, Hyderabad) (25 mg), were obtained from an acetonitrile solution (5 ml) on slow evaporation. Compound (II) was prepared by the reaction of two equivalents of (I) with one equivalent of $CoCl_2{\cdot}6H_2O$ in water–methanol (1:1 *v*/*v*). A drop of 0.1 *N* HCl was added and the reaction mixture was heated to 323 K in a temperature-controlled bath and stirred for 6 h. The resulting solution was cooled to room temperature and allowed to stand for 3 d for crystallization. On standing, blue–green crystals suitable for X-ray analysis were obtained.

### Compound (I)

*Crystal data*

$C_{18}H_{24}N_4O$
$M_r = 312.41$
Orthorhombic, *Pbca*
$a = 13.7930\ (12)$ Å
$b = 13.5544\ (12)$ Å
$c = 17.9574\ (16)$ Å
$V = 3357.2\ (5)$ Å$^3$
$Z = 8$
Mo $K\alpha$ radiation
$\mu = 0.08$ mm$^{-1}$
$T = 294$ K
$0.18 \times 0.16 \times 0.09$ mm

*Data collection*

Bruker SMART APEX CCD area-detector diffractometer
29671 measured reflections
2950 independent reflections
2559 reflections with $I > 2\sigma(I)$
$R_{int} = 0.039$

*Refinement*

$R[F^2 > 2\sigma(F^2)] = 0.043$
$wR(F^2) = 0.128$
$S = 1.07$
2950 reflections
214 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.19$ e Å$^{-3}$
$\Delta\rho_{min} = -0.15$ e Å$^{-3}$

**Table 1**
Selected geometric parameters (Å, °) for (I).

| | | | |
|---|---|---|---|
| C8—O1 | 1.2205 (18) | C15—N4 | 1.459 (2) |
| C8—N3 | 1.337 (2) | C17—N4 | 1.457 (2) |
| C9—N3 | 1.4591 (19) | N1—N2 | 1.3500 (18) |
| C11—N4 | 1.465 (2) | | |
| | | | |
| N3—C8—C7 | 116.40 (13) | C8—N3—C9 | 122.39 (14) |
| C7—N2—N1 | 106.02 (13) | C15—N4—C11 | 109.48 (13) |
| | | | |
| C9—C10—C11—N4 | 6.0 (2) | C16—C15—N4—C11 | 66.27 (16) |
| C13—C14—C15—N4 | 55.6 (2) | C12—C11—N4—C15 | 57.71 (17) |
| N4—C15—C16—C9 | −5.56 (19) | C10—C11—N4—C15 | −66.28 (16) |
| C14—C15—N4—C11 | −58.57 (17) | | |

**Table 2**
Hydrogen-bond geometry (Å, °) for (I).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| N3—H3N···N2 | 0.82 (2) | 2.42 (2) | 2.7591 (17) | 106.0 (17) |
| C5—H5···O1$^{i}$ | 0.93 | 2.60 | 3.520 (2) | 172 |
| C18—H18$A$···O1$^{ii}$ | 0.96 | 2.48 | 3.343 (2) | 149 |

Symmetry codes: (i) $-x+2, -y+2, -z$; (ii) $x-\frac{1}{2}, -y+\frac{3}{2}, -z$.

## Compound (II)

*Crystal data*

$[Co(C_{18}H_{25}N_4O)_2(H_2O)_2]Cl_4\cdot 12H_2O$
$M_r = 1079.79$
Triclinic, $P\overline{1}$
$a = 9.6311$ (9) Å
$b = 9.9794$ (9) Å
$c = 16.0133$ (14) Å
$\alpha = 92.611$ (1)°
$\beta = 103.449$ (1)°
$\gamma = 118.037$ (1)°
$V = 1299.5$ (2) Å$^3$
$Z = 1$
Mo $K\alpha$ radiation
$\mu = 0.61$ mm$^{-1}$
$T = 294$ K
0.12 × 0.10 × 0.07 mm

*Data collection*

Bruker SMART APEX CCD area-detector diffractometer
12536 measured reflections
4552 independent reflections
4220 reflections with $I > 2\sigma(I)$
$R_{int} = 0.020$

*Refinement*

$R[F^2 > 2\sigma(F^2)] = 0.038$
$wR(F^2) = 0.114$
$S = 1.10$
4552 reflections
355 parameters
8 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.51$ e Å$^{-3}$
$\Delta\rho_{min} = -0.21$ e Å$^{-3}$

**Table 3**
Selected geometric parameters (Å, °) for (II).

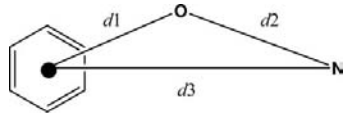
| | | | |
|---|---|---|---|
| Co1—O1$W$ | 2.0680 (16) | C9—N3 | 1.466 (3) |
| Co1—O1 | 2.0938 (14) | C11—N4 | 1.510 (3) |
| Co1—N2 | 2.1414 (16) | C15—N4 | 1.513 (3) |
| C8—O1 | 1.251 (2) | C17—N4 | 1.508 (3) |
| C8—N3 | 1.323 (3) | N1—N2 | 1.340 (2) |
| | | | |
| N3—C8—C7 | 119.69 (18) | C8—N3—C9 | 120.90 (18) |
| C7—N2—N1 | 107.67 (16) | C11—N4—C15 | 109.84 (18) |
| | | | |
| C9—C10—C11—N4 | 6.4 (3) | C12—C11—N4—C15 | 60.9 (2) |
| N4—C11—C12—C13 | −57.2 (3) | C10—C11—N4—C15 | −63.8 (2) |
| C13—C14—C15—N4 | 56.7 (3) | C14—C15—N4—C11 | −60.7 (3) |
| N4—C15—C16—C9 | −4.9 (3) | C16—C15—N4—C11 | 62.8 (2) |

**Table 4**
Hydrogen-bond geometry (Å, °) for (II).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| N3—H3N···Cl2$^{i}$ | 0.80 (3) | 2.56 (3) | 3.324 (2) | 161 (2) |
| N4—H4N···O4$W^{ii}$ | 0.83 (1) | 1.94 (1) | 2.761 (3) | 170 (3) |
| O1$W$—H1$W$···O6$W$ | 0.78 (3) | 1.99 (3) | 2.740 (3) | 163 (3) |
| O1$W$—H2$W$···O2$W$ | 0.85 (4) | 1.85 (4) | 2.696 (3) | 176 (3) |
| O2$W$—H3$W$···Cl1 | 0.82 (4) | 2.33 (4) | 3.145 (2) | 171 (3) |
| O2$W$—H4$W$···Cl2 | 0.89 (4) | 2.32 (4) | 3.204 (2) | 171 (3) |
| O3$W$—H5$W$···Cl1 | 0.88 (3) | 2.40 (3) | 3.280 (3) | 171 (4) |
| O3$W$—H6$W$···O5$W^{iii}$ | 0.89 (3) | 1.96 (2) | 2.719 (4) | 141 (3) |
| O4$W$—H7$W$···O6$W$ | 0.90 (3) | 2.02 (3) | 2.908 (4) | 170 (4) |
| O4$W$—H8$W$···Cl2 | 0.87 (4) | 2.34 (4) | 3.207 (2) | 172 (4) |
| O5$W$—H9$W$···Cl2 | 0.90 (5) | 2.28 (6) | 3.177 (4) | 178 (7) |
| O5$W$—H10$W$···Cl1 | 0.89 (4) | 2.50 (4) | 3.374 (4) | 168 (4) |
| O6$W$—H11$W$···O7$W$ | 0.88 (5) | 1.83 (5) | 2.699 (4) | 168 (4) |
| O6$W$—H12$W$···O3$W$ | 0.78 (3) | 1.91 (3) | 2.686 (4) | 178 (3) |
| O7$W$—H13$W$···Cl2$^{i}$ | 0.81 (4) | 2.37 (4) | 3.174 (3) | 175 (4) |
| O7$W$—H14$W$···Cl1$^{iv}$ | 0.75 (4) | 2.40 (4) | 3.151 (4) | 179 (4) |
| C9—H9···O4$W^{ii}$ | 0.98 | 2.51 | 3.371 (3) | 146 |
| C17—H17$C$···Cl1$^{v}$ | 0.96 | 2.74 | 3.601 (3) | 150 |
| C18—H18$C$···O1$^{vi}$ | 0.96 | 2.57 | 3.356 (3) | 139 |

Symmetry codes: (i) $x+1, y+1, z$; (ii) $x+1, y, z$; (iii) $-x, -y+1, -z+2$; (iv) $x, y+1, z$; (v) $-x+1, -y+1, -z+2$; (vi) $-x, -y+1, -z+1$.

**Table 5**
Selected topographical X-ray structural features of compounds (I) and (II) and other related structures (Å).




| | $d1$ | $d2$ | $d3$ | $D$ |
|---|---|---|---|---|
| (I) | 4.19 | 4.82 | 8.83 | 0.17 |
| (II) | 5.09 | 4.86 | 8.52 | 0.67 |
| Ondansetron HCl† | 4.30 | 6.35 | 9.72 | 0.94 |
| Palonosetron HCl‡ | 3.66 | 4.20 | 7.04 | 0.99 |
| (III)§ | 4.28 | 5.66 | 8.94 | 0.91 |

Notes: $d1$ is the distance between the aromatic ring centroid and linker carboxamide atom O1, $d2$ is the distance between atom O1 and the basic atom N4, $d3$ is the distance between the aromatic ring centroid and the basic atom N4, and $D$ is the deviation of the basic atom N4 with respect to the aromatic ring. † Chandra Mohan & Ravikumar (1995). ‡ Ravikumar & Sridhar (2007*b*). § Fludzinski *et al.* (1987).

All N-bound H atoms were located in difference Fourier maps and their positions and isotropic displacement parameters were refined. All C-bound H atoms were located in a difference density map, but

were positioned geometrically and included as riding atoms, with C—H distances in the range 0.93–0.98 Å and with $U_{iso}$(H) = 1.2$U_{eq}$(C) for the methyl groups and 1.2$U_{eq}$(C) otherwise. The water H atoms of (II) were located in difference Fourier maps and their positions were refined subject to distance restraints of O3*W*—H5*W* = O3*W*—H6*W* = O4*W*—H7*W* = O5*W*—H9*W* = O5*W*—H10*W* = 0.89 (1) Å and H5*W*···H10*W* = 2.19 (1) Å. The isotropic displacement parameters for the H atoms of O1*W*, O2*W*, O6*W* and O7*W* were refined, while those of the H atoms of all other water molecules were set at $U_{iso}$(H) = 1.2$U_{eq}$(O). To avoid close contacts between the water H atoms a mild antibumping restraint was applied.

For both compounds, data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *DIAMOND* (Brandenburg & Putz, 2005) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3133). Services for accessing these data are described at the back of the journal.

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